Journal of the American College of Cardiology Vol. 55, No. 24, 2010

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.01.051

EDITORIAL COMMENT

More Progression Toward Regression?

Beyond Low-Density Lipoprotein Cholesterol Lowering*

Basil S. Lewis, MD, David A. Halon, MB, ChB

Haifa, Israel

The new millennium has ushered in a new era in our understanding and treatment of atherosclerotic vascular disease. Using new imaging technologies, we have windows into the vasculature: intravascular ultrasound (IVUS) and related technologies (virtual histology [VH], optical coherence tomography), carotid intima-media thickness, calcium scoring, and noninvasive angiography using multislice computed tomography (CT), and magnetic resonance imaging. Regarding treatment and prevention, we have clear evidence that lowering low-density lipoprotein cholesterol (LDL-C) and modulating high-density lipoprotein cholesterol (HDL-C) may limit the progression of vascular disease and improve clinical outcome, and that more intensive lowering of LDL-C levels may be associated with regression of atheromatous plaque (1).

See page 2736

In this issue of the *Journal*, Bayturan et al. (2) focus on the challenging question of plaque progression in patients with what is currently accepted as well-treated LDL-C, an on-treatment LDL-C level of <70 mg/dl. Using serial IVUS measurements, they report clinical predictors of progression (>5% increase in percent plaque volume as percent of segmental arterial volume) in 951 such patients studied in 7 different clinical trials. Given the possible questions regarding conclusions based on groups of patients treated with very different pharmacotherapeutic agents, the findings in the 200 (21%) progressors compared with the 751 (79%) nonprogressors are nonetheless hypothesis generating and, indeed, in keeping with clinical instinct and previous knowledge. Disease progression despite low LDL-C levels was, not surprisingly, independently associated with the presence of diabetes mellitus, higher systolic blood pressure, smaller increase in HDL-C, and a smaller decrease in apolipoprotein B (apoB) levels. Smaller baseline absolute and percent atheroma volume predicted progression but was more difficult to explain, perhaps a mathematical finding when percent change rather than absolute change was reported. Assessing progression solely as a percentage of baseline plaque volume may not be the ideal correlate for late outcome events.

The findings redefine and confirm therapeutic targets beyond LDL-C lowering on which to focus if we are to halt progression of atheromatous disease. However, 2 major issues need to be considered. First, we currently do not have a clear treatment strategy for these targets. Aggressive glycemic management in diabetic patients is being reevaluated after the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study, and the VA Diabetes Trial (3), and the target management level may need tailoring on an individual basis (4). It is quite likely that the exact pharmacotherapeutic agent may be crucial with regard to clinical outcome. In the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study (5), pioglitazone was associated with a greater than expected change in atheroma volume. With regard to HDL-C, we do not yet have an effective treatment for raising HDL-C that has clear benefit on clinical outcome. Niacin treatment needs more definitive outcome data, although promising (6), and the first major trial of a cholesteryl ester transfer protein inhibitor to raise HDL-C was associated with side effects and increased mortality (7). New drugs acting on apoB and other lipid fractions all need to be tested mechanistically as well as in terms of clinical outcome events.

Second, and beyond the provision of optimal therapy for accepted risk factors, is another not less important unknown—the relation between plaque volume, plaque characteristics, and clinical outcome events. Although plaques that rupture and cause an acute event are almost always large (8,9), specific plaque characteristics may have greater predictive value. Recent evidence from studies using VH-IVUS shows that characteristics of plaque are related to the major risk factors diabetes, hypertension, and serum LDL-C and HDL-C levels (10), and that the ratio of necrotic core to dense calcium seems to correlate with LDL-C and the total cholesterol/HDL-C ratio (11). In patients with stable angina pectoris, serial coronary VH-IVUS studies after statin therapy showed that total plaque volume and fibrofatty plaque volume decreased, and fibrous plaque volume increased (12). There may be drug differences: fibrofatty plaque decreased with pitavastatin in correlation with LDL-C levels but not with atorvastatin (13). It appears that plaque characteristics by IVUS and VH-IVUS may indeed relate to outcome events. In the

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Department of Cardiovascular Medicine, Lady Davis Carmel Medical Center, and the Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial, the combination of a large nonculprit plaque burden, small luminal area (≤4 mm^2) and large necrotic core without visible cap (combination found in 15% of this acute coronary syndrome population) was associated with an almost 10-fold increase in major adverse cardiovascular events (14). We need more in vivo information if we are to piece together the missing links in the chain between plaque volume and a clinically relevant event. Determinants of plaque volume may be different from those triggering an acute event. Indeed, although, in the present study, changes in C-reactive protein or LDL-C itself did not predict plaque progression, the clinical arena suggests that these may be important in predicting, determining, or triggering clinical events (15–17).

Notwithstanding the limitations in our knowledge, the present paper, as a form of "GPS," suggests that we appear to be at least somewhat on track in our fight to halt and perhaps reverse the pathology and progression of atherosclerotic vascular disease. By focusing on the 20% who progress "beyond LDL-C lowering," we may better improve therapeutic strategies for all.

Reprint requests and correspondence: Dr. Basil S. Lewis, Department of Cardiovascular Medicine, The Heart Hospital at Lady Davis Carmel Medical Center, 7 Michal Street, Haifa 34362, Israel. E-mail: lewis@tx.technion.ac.il.

REFERENCES

1. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006;295:1556–65.
2. Bayturan O, Kapadia S, Nicholls SJ, et al. Clinical predictors of plaque progression despite very low levels of low-density lipoprotein cholesterol. J Am Coll Cardiol 2010;55:2736–42.
3. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events. Implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. J Am Coll Cardiol 2009;53:298–304.
4. Greenfield S, Billimek J, Pellegrini F, et al. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes. Ann Intern Med 2009;151:854–60.
5. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008;299:1561–73.
6. Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. N Engl J Med 2009; 361:2113–22.
7. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007;357: 2109–22.
8. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 1997;336:1276–82.
9. Narula J, Garg P, Achenbach S, Motoyama S, Virmani R, Strauss HW. Arithmetic of vulnerable plaques for noninvasive imaging. Nat Clin Pract Cardiovasc Med 2008;5 Suppl 2:S2–10.
10. Philipp S, Bose D, Wijns W, et al. Do systemic risk factors impact invasive findings from virtual histology? Insights from the international virtual histology registry. Eur Heart J 2010;31:196–202.
11. Missel E, Mintz GS, Carlier SG, et al. In vivo virtual histology intravascular ultrasound correlates of risk factors for sudden coronary death in men: results from the prospective, multi-centre virtual histology intravascular ultrasound registry. Eur Heart J 2008;29: 2141–7.
12. Nasu K, Tsuchikane E, Katoh O, et al. Effect of fluvastatin on progression of coronary atherosclerotic plaque evaluated by virtual histology intravascular ultrasound. J Am Coll Cardiol Intv 2009;2: 689–96.
13. Toi T, Taguchi I, Yoneda S, et al. Early effect of lipid-lowering therapy with pitavastatin on regression of coronary atherosclerotic plaque. Comparison with atorvastatin. Circ J 2009;73:1466–72.
14. Stone GW. PROSPECT: a natural history study of atherosclerosis using multimodality intracoronary imaging to prospectively identify vulnerable plaque. Paper presented at: Transcatheter Cardiovascular Therapeutics, September 21–25, 2009; San Francisco, CA.
15. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001;344:1959–65.
16. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
17. Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes: from the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial. J Am Coll Cardiol 2009;54:2358–62.

Key Words: very low LDL-C levels ■ residual risk factors ■ apolipoprotein B ■ plaque progression.